Remarks

On August 23, 2007, the Office mailed a Notice of Non-Compliant Amendment indicating the amendment filed by Applicants on July 18, 2007 was not in compliance with 37 C.F.R. 1.173(b)(2). Applicants filed an amendment on August 31, 2007, in response to the 23 August Notice indicating which claims had been changed or added by the amendment and using the designations of "amended", "twice amended", etc., required by rule 173(b) and (d) and indicating changes or additions to the claims relative to the patent claims and not the last amendment as required by rule 173.

On September 4, 2007, the Office mailed a second Notice of Non-Compliant Amendment indicating that Applicants 31 August Amendment was not in compliance with 37 C.F.R. 1.121 because it did not include a complete listing of the claims. In an attempt to comply with both rules 173 and 121, Applicants have included a complete listing of the claims. Only claims that have been amended by this amendment are designated using the designations of "amended", "twice amended", etc., as required by rule 173. However, the listing of the claims shows all deletions and additions made to the claims to date relative to the claims as presented in the patent and not the previous amendment.

This paper is further filed in response to the Office Action mailed January 18, 2007. Claims 1-104 are pending. By this amendment, claims 1, 8, 15, 37, 44, 51, 56, 57, 58, 67, 69, 78, 80, 81, 90 and 92 are amended.

The items raised in the 18 Office Action are addressed in the remarks below.

I. Interview Summary

An interview was conducted with the Examiner on July 17, 2007 during which the examiner's rejections of claims 1—104 as being based upon a defective reissue oath under 35 U.S.C. § 251, as failing to comply with the written description requirement under 35 U.S.C. § 112, as being anticipated by prior art under 35 U.S.C. § 102(e), and as being unpatentable over prior art under 35 U.S.C. § 103. An agreement was reached in regard to the rejection based upon a defective oath, but no agreement was reached in regard to the rejections under 35 U.S.C. §§ 112, 102 and 103.

II. Oath / Declaration

The Examiner rejected claims 1-104 as being based upon a defective reissue oath under 35 U.S.C. § 251. During the interview, the Examiner withdrew the following grounds for this rejection: "the stated error in the oath does not reflect a broadening reissue."

A supplemental Oath/Declaration will be filed and will correct the error of the missing mailing address of one of the inventors.

III. Claim Rejections – 35 U.S.C. § 112

Claims 1—104 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Support for either the agent or a fluid delivery vehicle producing a disruption in the vessel is found in the specification at column 3, lines 8—16:

> By retroinfused is meant that a physiologically acceptable flowable formulation of the active agent is introduced into the circulatory or vascular system of the host in a retrograde manner, i.e. in a manner that is against the normal blood flow direction in the vascular or circulatory location (i.e. vascular deposition site) in which the agent formulation is administered. Thus, the flowable agent formulation is administered via a retrograde infusion technique;

and at column 5, lines 32—41:

> In another preferred embodiment of the subject methods, the flowable formulation of the active agent is introduced into the vascular deposition space in a manner such that the mechanical stress is of sufficient magnitude to provide for actual disruption of the vessel wall. By disruption of the vessel wall is meant that the integrity of the wall is compromised such that actual passageways appear between the interior of the vessel and regions beyond the inner wall surface, i.e. between the vascular deposition site and the target interstitial space.

Accordingly, Applicants respectfully request withdrawal of the rejection of those claims under section 112.

IV. Claim Rejections – 35 U.S.C. § 102

Claims 1-3, 7-11, 13-19, 21-23, 29-39, 43-47, and 49-100 were rejected under 35 U.S.C. § 102(e) as being anticipated by Wolff et al. (USP 6,867,196). Applicants respectfully request reconsideration of this rejection.

Independent claims 1, 8, 15, 37, 44, 51, 56, 67, 78, and 90 have been amended to clarify that a disruption in a vessel comprises a passageway created in a wall of the vessel. Support for this amendment can be found at At column 5, lines 32—41:

> In another preferred embodiment of the subject methods, the flowable formulation of the active agent is introduced into the vascular deposition space in a manner such that the mechanical stress is of sufficient magnitude to provide for actual disruption of the vessel wall. **By disruption of the**

> **vessel wall is meant** that the integrity of the wall is compromised such that actual passageways appear between the interior of the vessel and regions beyond the inner wall surface, i.e. between the vascular deposition site and the target interstitial space.

Wolff, however, only describes enhanced delivery through natural channels (and not unnatural, i.e. disruptive channels, as provided in amended claims). In Wolff, at column 5, lines 31-38, the specification describes "large pores" existing in blood vessel walls and the use of pressure to enhance the delivery of DNA transfer through these large pores.

> This implies that plasmid DNA is capable of crossing microvascular walls by stringing through the large pores. Pressure may be one method for transfection of liver and skeletal muscle and may enhance plasmid DNA transfer by opening the endothelial barrier. Raising the intravascular hydrostatic pressure transiently increases water flow through the large pores and thereby forces the extravasation of plasmid DNA.

Thus, the delivery of DNA to a tissue bed is through existing blood vessel pores and not through disruption of the integrity of the vessel walls as claimed. The specification further describes delivery of DNA through vessel pores and the enhancement of such pores:

> We suggest that the rate of plasmid DNA extravasation can be increased by enhancing fluid convection through the large pores by raising the transmural pressure difference in selective regions. (Column 5, lines 49-53).
>
> For instance, VEGF in high doses significantly enhances fluid leakage, probably by enlarging pore size. (Column 5, lines 59-61).
>
> The hypothesis is that high intravascular a predetermined volume in a predetermined period of time is required to initiate flow through the pores. (Column 6, lines 40-42).

Wolf also describes increasing pressure for delivery through the microcapillary bed, also a pre-existing, i.e. natural channel of delivery from blood vessel to tissue. See, e.g., column 6, lines 25-26: "It may very well be that the microcapillary bed allows efficient delivery."

Moreover, Wolff does not wish to cause tissue damage. See, e.g., column 7, lines 2-8:

> By creating a feedback between the intravenous pressure at the site of injection and the injection pump, a system can be created that automatically senses the target bed size and inject the proper amount of transfection solution. By limiting the injection volume per time unit, minimal tissue damage is incurred.

Further, in col 9 lines 30-45, Wolff describes an "intravascular" route of administration as "within tubular structures…connected to a tissue or organ" and "within the cavity of the tubular structures, a bodily fluid flows to or from the body part." All these fluid channels are pre-existing and natural channels. The permeability of these channels can be modified, as Wolff described in column 11 by hydrostatic pressure, osmotic pressure, chemically, or biological agent, but these permeability changes simply increase the delivery of agents through natural channels in the vessel wall. Blood vessels are already somewhat permeable, Wolff simply describes enhancing this.

Accordingly, because the Wolff et al. patent fails to disclose every element of the claims at issue, those claims are patentable over and above the Wolff et al. patent. Applicants respectfully request withdrawal of the rejection of those claims under section 102(e).

IV. Claim Rejections – 35 U.S.C. § 103

The Examiner rejected claims 1, 4-6, 8, 12, 15, 20, 24, 28, 37, 40-42, 44, 48, 51, 56-59, 61-82, 84-93 and 95-104 under 35 U.S.C. § 103(a) as being unpatentable for obviousness over the Wolff et al. patent in vie of Makower et al (US 2002/0179098). As noted above, Wolff et al. explicitly teach not to damage the vessel or other tissue, as would occur if the vessels are disrupted. In addition, as noted above, the Wolff et al. patent fails to disclose, teach, or suggest methods that include disruption of the vessel, or the

administration of energy to the vessel. Because these limitations are not met by the art relied upon by the Examiner, there has been no prima facie showing of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection of these claims under section 103(a).

SPECIFICATION SUPPORT AND STATUS OF CLAIMS

Specification support for all of the amendments and new claims is listed in the "Statement of Status / Support for Changes to Claims (Amendment Dated July 18, 2007)" submitted with Applicants 18 July 2007 Amendment. No new matter is added by this amendment.

CONCLUSION

In view of the foregoing, it is submitted that the claims presented in this reissue application define patentable subject matter to which Applicant is entitled. Accordingly, consideration and allowance of the reissue application is requested.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 15-0665.

Respectfully submitted,

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